



HOKKAIDO UNIVERSITY

Title	Environmental Regulation of Bile Acid Metabolism and the Pathophysiological Significance of 12-Hydroxylated Bile Acids
Author(s)	横山, 史佳
Description	この博士論文の全文は利用可能日以降に公開されます。
Degree Grantor	北海道大学
Degree Name	博士(農学)
Dissertation Number	乙第7245号
Issue Date	2026-06-30
DOI	https://doi.org/10.14943/doctoral.r7245
Doc URL	https://hdl.handle.net/2115/100104
Type	doctoral thesis
File Information	Fumika_Yokoyama_abstract.pdf, 論文内容の要旨 https://creativecommons.org/licenses/by/4.0/



学 位 論 文 内 容 の 要 旨

博士の専攻分野の名称： 博 士（農学）

氏名 横 山 史 佳

学 位 論 文 題 名

Environmental Regulation of Bile Acid Metabolism and the Pathophysiological Significance of 12-Hydroxylated Bile Acids

(環境要因による胆汁酸代謝の調節と 12 水酸化胆汁酸の病態生理学的意義)

Bile acids (BAs) function not only as digestive surfactants but also as signaling molecules that regulate various aspects of metabolism. Among the diverse BA species, 12-hydroxylated (12OH) BAs have drawn attention as potential contributors to metabolic dysfunction, yet their specific physiological actions and pathophysiological consequences remain to be elucidated. In this study, it was investigated how environmental factors regulate BA metabolism and shed light on the fundamental mode of action by which 12OH BAs induce metabolic dysfunctions, especially hepatic lipid accumulation in rats.

1. Modulation of BA metabolism by environmental factors

It is examined how meal feeding and cellular stress responses modulate BA secretion and composition within the enterohepatic circulation. There was a rapid increase in 12OH BA concentrations, particularly taurocholic acid (TCA), in the bile-pancreatic fluid and liver tissue within 1 hour of refeeding following food deprivation. The postprandial elevation of enterohepatic TCA concentration correlated positively with hepatic mRNA expression of hydroxymethylglutaryl-CoA reductase, the rate-limiting enzyme in cholesterol synthesis, suggesting that 12OH BAs function as metabolic mediators in cholesterol synthesis under nutrient-rich conditions. Tunicamycin, an endoplasmic reticulum stress inducer, elevated systemic BA levels, which were accompanied by increased expression of hepatic efflux transporters (ATP binding cassette subfamily C member 3 and 4), suggesting that cellular stress responses dynamically alter BA homeostasis. These findings indicate that BA metabolism dynamically responds to environmental changes, with 12OH BAs playing a central role in these fluctuations.

2. Pathophysiological consequences of elevated 12OH BAs

A 12OH BA-dominant environment was established through chronic dietary supplementation with cholic acid (CA) at 0.5 g CA/kg diet, which reproduces in vivo BA

metabolism under nutrient-rich conditions including high-fat diet feeding. This environment induces various features of metabolic dysfunction, such as hepatic lipid accumulation, leaky gut, and hypertension. It was investigated whether 12OH BAs influence insulin secretion in glucose tolerance tests. In addition, the underlying mechanisms were explored in hepatic lipid accumulation induced by the 12OH-dominant environment.

Systemically elevated 12OH BAs impaired glucose-stimulated insulin secretion in the absence of incretin involvement. While no difference in insulin secretion was observed in response to oral glucose administration between control and CA-fed rats, a significant reduction was observed in the secretion of insulin and C-peptide despite maintained glucose tolerance in response to intraperitoneal glucose administration. This impairment occurred without pancreatic lipid accumulation or islet loss, suggesting that the effects of 12OH BAs on β -cells are not mediated by lipotoxicity. The different responses between oral and intraperitoneal glucose administrations suggest that 12OH BAs suppress glucose-stimulated insulin secretion specifically in the absence of incretin. To understand the mechanism that mediates hepatic lipid accumulation, it is necessary to consider lipogenesis, fatty acid oxidation, lipid incorporation, and lipid secretion in hepatocytes. Among them, it was already known that lipid incorporation does not participate in the 12OH BA-induced hepatic lipid accumulation, and that fatty acid oxidation is retarded. In this study, involvement of the remaining two events, such as very-low-density lipoprotein (VLDL) secretion and de novo lipogenesis, was investigated. In tyloxapol-induced lipoprotein accumulation studies, VLDL secretion was suppressed only in the presence of insulin. This synergistic suppression of VLDL secretion suggests an enhancement of lipid storage in hepatocytes, especially in postprandial conditions by 12OH BAs.

Lipogenesis evaluated by using stable isotope was detected only in a postprandial period in a refeeding study, but not in an ad libitum feeding. Furthermore, comparison of the responses between 1-week versus 12-week CA supplementation studies revealed that the lipogenesis enhancement requires relatively prolonged exposure to 12OH-dominant environment, as the hepatic lipid accumulation occurred even after 1 week without detectable lipogenesis. These findings suggest that VLDL suppression and lipogenesis participate in the 12OH BA-induced hepatic lipid accumulation in a time-dependent manner.

In conclusion, BA metabolism is highly responsive to environmental factors such as nutrient availability and cellular stress, and 12OH BAs act as mediators to develop several features of metabolic disorders. Postprandial and stress-induced elevations of 12OH BAs in the body, particularly TCA, contribute to metabolic dysfunction by impairing insulin secretion independently of incretin signaling and by promoting hepatic lipid accumulation. Mechanistically, 12OH BA-induced hepatic lipid accumulation arises through a time-dependent combination of insulin-dependent suppression of VLDL secretion and a subsequent enhancement of de novo lipogenesis. Collectively, these findings suggest 12OH BAs as critical regulators linking environmental conditions to metabolic dysregulation, especially hepatic lipid accumulation, under nutrient-rich conditions.